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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Srivastava *et al.*	Confirmation No.: 1804
Serial No.: 09/668,724	Art Unit: 1642
Filed: September 22, 2000	Examiner: REDDIG, Peter J.
For: ALPHA (2) MACROGLOBULIN RECEPTOR AS A HEAT SHOCK PROTEIN RECEPTOR AND USES THEREOF	Attorney Docket No: 8449-128-999 CAM No.: 708584-999127

DECLARATION OF DR. HANS-GEORG RAMMENSEE UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, HANS-GEORG RAMMENSEE, do declare and state as follows:

1. I am a citizen of Germany residing at Sommerhalde 3 72070 Tübingen, Germany.

2. I am a member of the Scientific Advisory Board of Antigenics, Inc., exclusive licensee of the invention described and claimed in United States Patent Application No. 09/668,724.

3. I am currently chair of immunology at the University of Tübingen in Germany. From 1987 to 1993 I served at the Max Planck Institute for Biology, where I was head of the laboratory for immunology. From 1993 to 1996, I was head of the department of tumor virus-immunology, German Cancer Research Center, Heidelberg, and was on the faculty of theoretical medicine. From 1992 until 1997, I was a member of the "Hinterzartener Kreis," a committee of the German Research Council. At present, I am a member of the Evaluation Committee for the Cooperation Program in Cancer Research between DKFZ (Heidelberg) and the Ministry of Science (Israel). For the past 14 years, I have been co-editor of Immunogenetics and, since 1991, co-editor of European Journal of Immunology.

4. My academic and technical experience and honors are set forth in my *curriculum vitae*, attached hereto as **Exhibit A**.

5. I have reviewed and I am familiar with the above-identified application. The present application teaches that heat shock proteins (also referred to herein as "hsp") bind to a specific receptor on antigen presenting cells, the α2M receptor, also referred to in the art as "CD91," and that receptor binding is required for the immune response generated by heat shock proteins. Specifically, data in the specification, discussed in paragraph 10 below, demonstrate that antagonists of hsp-α2M receptor binding effectively block antigen-specific T cell activation by heat shock proteins.

6. I have reviewed and I am familiar with the pending claims in the above-identified application and with the Office Action dated September 21, 2006 in connection with this application. I have been informed and believe that the claims are rejected, in part, based upon a contention that one could not reasonably predict that the claimed method will function in humans to inhibit an immune response so as to treat an autoimmune disease or disorder, in view of the alleged absence of objective evidence of the foregoing.

7. I have reviewed and am familiar with the technical data disclosed in the above-identified application, as well as the data disclosed in the published references, Exhibits 1-11. These data demonstrate the following, as discussed in more detail below:

(1) the immune response generated by heat shock proteins is mediated by antigen-specific T cell activation, which is a fundamental mechanism for immunity generally, and which is directly involved in the pathogenesis of autoimmune diseases, such that compounds that inhibit T cell activation are reasonably predicted to be useful for the treatment of an autoimmune disease or disorder;

(2) each of the compounds recited in the claims interferes with (*i.e.*, is an antagonist of) the interaction between hsp and an α2M receptor, and each has either been shown to inhibit the immune response generated by heat shock proteins (*i.e.*, anti-α2M receptor antibodies), or is reasonably predicted to do so based on its ability to interfere with the interaction between hsp and an α2M receptor (*i.e.*, anti-hsp antibodies and an hsp-binding fragment of the α 2M receptor fragment); and

(3) an antagonist of ligand-α2M receptor binding, gp96, being itself an hsp, has been demonstrated to delay the onset of autoimmune disease in two well-known animal models, the experimental autoimmune encephalomyelitis ("EAE") model, and the non-obese diabetic ("NOD") mouse model.

8. It was known in the art at June 2000 that mammalian heat shock proteins (also referred to in the literature as "stress proteins") can elicit an antigen-specific immune response against peptide complexed to the heat shock protein. This immune response is characterized by a peptide-specific activation of T cells, which was measured either in *vitro* as a specific T cell response against the peptide, or *in vivo* as protective immunity against transplanted tumor cells in the mouse tumor transplantation model (see Suto and Srivastava, 1995 "A mechanism for the specific immunogenicity of heat shock protein-chaperoned peptides," Science 269:1585-1588 ("Suto") at p. 1585, col. 1, enclosed as **Exhibit 1**). The importance of T cell activation in generating anti-tumor immunity in this model system was already well-established at the time of filing (see *e.g.*, Abbas, Lichtman, and Pober, 1991 Cellular and Molecular Immunology, W.B. Saunders Co., Philadelphia (Chapters 15-18) ("Abbas") at p. 347, col. 1 para. 3; see also p. 338-340, enclosed as **Exhibit 2**, discussing the T cell response generated against tumor-specific transplantation antigens in this model system).

9. T cell activation is an important mechanism for immunity generally. For example, $CD8^+$ T cells are the principal mechanism of specific immunity against established viral infections (see Abbas at p. 310, col. 1, para. 2-3) and the rejection of transplanted allografts is mediated by $CD8^+$ and $CD4^+$ T cells (see Abbas at p. 320, col. 1 to col. 2). With respect to autoimmune diseases and disorders, T cell responses are directly involved in causing tissue damage in a number of organ-specific autoimmune diseases (see e.g., Janeway, Travers, Walport, and Shlomchick, 2001 Immunobiology, 5th ed., Garland Publishing, New York (p. 6-7) ("Janeway") at p. 7, para. 2, enclosed as **Exhibit 3**). The direct involvement of T cells in the pathogenesis of autoimmune diseases has also been demonstrated in two well-known animal models of autoimmunity, the EAE model, which is a mouse model for human multiple sclerosis and human encephalomyelitis, and the NOD model, which is a mouse model for insulin-dependent diabetes mellitus. Pathogenesis in these models is caused by autoreactive $CD4^+$ and $CD8^+$ T cells against specific antigens. In the NOD model, pathogenesis is caused by autoreactive $CD4^+$ and $CD8^+$ T cells against

antigens of pancreatic islet cells (see *e.g.*, Chandawarkar et al., 2004 "Immune modulation with high-dose heat shock protein gp96: therapy of murine autoimmune diabetes and encephalomyelitis," Int'l Immunol. 16:315-324 ("Chandawarkar") at p. 619, col. 1, lines 1-2, enclosed as **Exhibit 4**; and Abbas at p. 367, Box 18-3), and in the EAE model, pathogenesis is caused by autoreactive $CD4^+$ and $CD8^+$ T cells against myelin basic protein (see *e.g.*, Steinman, L. 2001 J. Exp. Med., "Myelin-specific $CD8^+$ T cells in the pathogenesis of experimental allergic encephalitis and multiple sclerosis," 194:F27-F30 ("Steinman") at p. F27, col. 1, para. 1, and col. 2, para. 2, enclosed as **Exhibit 5**). The immune response generated by mammalian heat shock proteins also comprises antigen-specific $CD8^+$ and $CD4^+$ T cells (see *e.g.*, SenGupta et al., 2004 J. Immunol., "Heat shock protein-mediated cross-presentation of exogenous HIV antigen on HLA Class I and Class II," 173:1987-1993 ("SenGupta") at p. 1987, col. 2 first para., enclosed as **Exhibit 6**, and references 17-19 cited therein). Accordingly, the immune response generated by mammalian heat shock proteins, as an antigen-specific T cell response, is an important mechanism of immunity generally, and could be, presumably, an important mechanism of pathogenesis in autoimmune diseases and disorders. Since T cell activation is directly involved in the pathogenesis of autoimmune diseases, compounds that inhibit T cell activation in the context of an autoimmune disease or disorder would reasonably be expected to have efficacy in treating the autoimmune disease or disorder.

10. The present application presents specific technical data demonstrating that antagonists of hsp-α2M receptor binding effectively block antigen-specific T cell activation by heat shock proteins. This is demonstrated for a number of compounds which interfere with the interaction of the α2M receptor with a heat shock protein, including antibodies (*i.e.*, anti-α2M receptor antibodies), and a competitive inhibitor of heat shock protein binding to the α 2M receptor (*i.e.*, α2M). Specifically, the specification demonstrates that antiserum against the 80 kilodalton hsp-binding fragment of the α2M receptor inhibited T cell activation by gp96 (see the specification at p. 72, line 29 to p. 73, line 8 and Fig. 2B). The specification also demonstrates that increasing concentrations of α2M, a recognized ligand of the α2M receptor, effectively inhibited T cell activation by heat shock proteins (see the specification at p. 73, lines 20-24, and Fig. 4). These results show that compounds which interfere with the interaction of the α2M receptor and a heat shock protein are able to

block the immune response, *i.e.*, the antigen-specific T cell activation, generated by heat shock proteins, which is an important mechanism of immunity.

11. The assay used in the specification of the present application to measure an immune response is an assay for T cell activation, referred to as a "re-presentation" assay. The name "re-presentation" reflects the common knowledge at June 2000 that the peptide complexed to heat shock protein does not directly stimulate T cell activation but instead must first be taken up and re-presented to the T cells by antigen presenting cells in complex with MHC molecules (see Suto, **Exhibit 1**, cited and explained by Binder and Srivastava, 2004 "Essential Role of CD91 in re-presentation of gp96-chaperoned peptides," Proc. Natl. Acad. Sci. U.S.A. 6128-6133 ("Binder 2004") at p. 6130, col. 1 para. 2 and col. 2 para. 2, enclosed as **Exhibit 7**). This was first demonstrated by data showing that antigen complexed with heat shock protein was channeled into the endogenous antigen-processing pathway of antigen presenting cells, re-presented by Class I MHC molecules, and recognized by cytotoxic T cells (see Suto, **Exhibit 1**, *supra*). It has also been demonstrated that antigen complexed with heat shock protein is re-presented by Class II MHC molecules (see SenGupta, **Exhibit 6**, at p. 1987, col. 1, para. 1, and references cited therein). However, the quantitative measure of this assay is one of T cell activation, which is a measure of an immune response, not of peptide bound to MHC molecules. Further, *in vitro* activity as determined by re-presentation assays has been demonstrated to correlate with *in vivo* activity in the induction of an immune response, as I discuss below.

12. The technical data in the specification of the present application demonstrating that antagonists of hsp-α2M receptor binding inhibit the immune response generated by heat shock proteins are confirmed and extended by the post-filing evidence provided in four documents: (1) Binder et al., 2002 "Naturally formed or artificially reconstituted non-covalent alpha-2-macroglobulin-peptide complexes elicit CD91-dependent cellular immunity," Cancer Immunity 2:16-23 ("Binder 2002"), enclosed as **Exhibit 8**, (2) Binder 2004 (**Exhibit 7**), (3) Basu et al., 2001 Immunity, "CD91 is a common receptor for heat shock proteins gp96, hsp90, hsp70, and calreticulin," 14:303-313 ("Basu"), enclosed as **Exhibit 9**, and (4) Chandawarkar (**Exhibit 4**). Binder 2002 demonstrates that an anti-CD91 antibody effectively blocked the anti-tumor immunity generated by heat shock proteins *in vivo* in the mouse tumor transplantation model system (see Binder 2002 at p. 19 and Fig. 3). As discussed above, anti-tumor immunity in this

model system is known to involve T cell activation. Mice were immunized with gp96-peptide complexes plus either the anti-CD91 antibody or an isotype control antibody. Additional antibody was administered at the same site each day for two days after each immunization. Live tumor cells were injected intradermally one week after the last immunization and tumor growth (volume) was measured over a period of about 20 days. As shown in Figure 3, top left panel, of Binder 2002, mice immunized with gp96-peptide complexes and the isotype control antibody experienced very little tumor growth. In contrast, mice immunized with gp96-peptide complexes and the anti-CD91 antibody showed considerable tumor growth, demonstrating that the anti-CD91 antibody blocked the protective immunity of the gp96-peptide complexes (see Figure 3, bottom left panel). Binder 2004 confirms these results in another *in vivo* tumor transplantation model system using a polyclonal anti-CD91 antibody and gp96-peptide complexes purified from the cancer cells (see Binder 2004 at p. 6131, col. 2, para. 3, and Fig. 5 at p. 6133). As shown in Figure 5 of Binder 2004, top three panels, all of the mice in each of three groups receiving either (1) PBS, (2) anti-CD91 antibody alone, or (3) control antibody alone experienced significant tumor growth during the 20 days of the experiment. In contrast, mice receiving gp96 complexes purified from the cancer cells showed very little tumor growth (see Fig. 5, middle row, left panel). This anti-tumor immunity was effectively inhibited by co-administration of the anti-CD91 antibody with the gp96 complexes, but not by co-administration of the control antibody (see Fig. 5, middle row, second and third panels from left). The bottom panels in Figure 5 shows that gp96 complexes isolated from liver had no effect on tumor growth, as expected, since such complexes do not carry the tumor antigens which provide immunity. Further, these *in vivo* data in Binder 2002 and Binder 2004, combined with the *in vitro* data in the specification of the present application showing that anti-CD91 antibodies inhibit an antigen-specific T cell response in an *in vitro* re-presentation assay (see the specification at p. 72, line 29 to p. 73, line 8 and Fig. 2B), demonstrate a correlation between the inhibitory activity of anti-α2M receptor antibodies in an *in vitro* re-presentation assay and their ability to inhibit an immune response *in vivo*.

13. Binder 2004 also demonstrates that other antagonists of hsp- α2M receptor binding, *i.e.*, the α2M receptor ligands RAP and α2M, effectively block the immune response generated by heat shock proteins. RAP and α2M inhibited T cell activation by gp96-complexed peptide in an *in vitro* re-presentation assay, as shown in Fig. 2 at page 6130. In a further *in vivo* re-presentation experiment, antigen presenting cells were isolated

from the draining lymph nodes of mice which had been immunized with gp96-peptide complexes alone or in the presence of either α2M or anti-CD91 antibody (see Binder 2004 at p. 6130, col. 2 to p. 6131, col. 1, and Fig. 3). The isolated antigen presenting cells were then co-cultured with T cells and T cell activation was measured. As shown in Figure 3, the presence of compounds that interfere with the heat shock protein-α2M receptor interaction, during immunization with heat shock proteins, effectively blocked the antigen-specific activation of T cells. Thus, Binder 2004 shows a correlation between the inhibitory activity of a compound, α2M, in an *in vitro* re-presentation assay and its *in vivo* ability to inhibit an immune response.

14. Basu (**Exhibit 9**) provides additional data demonstrating that compounds that bind to the α2M receptor, specifically heat shock proteins, α2M, and anti-α2M receptor antibody, are effective antagonists of the immune response generated by heat shock proteins. Basu demonstrates that α2M and an anti-α2M receptor antibody (two compounds that interfere with the interaction between heat shock protein and the α2M receptor) both effectively blocked re-presentation of the antigenic peptide by each of the heat shock proteins, gp96, hsp90, hsp70, and calreticulin (see Basu at p. 305, col. 2, para 4, to p. 306, col. 2, para. 1, and Fig. 5B and 5C). Further, in Basu, antigen presenting cells were pulsed with gp96 complexed with antigenic peptide (AH1/19) in the presence of increasing concentrations of either gp96, hsp90, hsp70, or serum albumin, and T cell activation was measured by cytokine release *in vitro* (see Basu at p. 305, col. 2, para. 2-3, and Fig. 5A; note that although the competing heat shock proteins are referred to as "uncomplexed" in the legend to Fig. 5A, this is meant only with respect to the antigenic peptide, AH1/19, and not other, unrelated peptides, see e.g., Basu at p. 305, col. 2, para. 2). The results demonstrated a dose-dependent inhibition of T cell activation with increasing concentrations of each of the inhibitors, gp96, hsp90, or hsp70. Thus, Basu provides a further demonstration that antagonists of the interaction between heat shock protein and the α2M receptor effectively inhibit an immune response and that gp96, hsp90, hsp70, α2M, and an antibody against the α2M receptor are all effective antagonists in this context. Chandawarkar (**Exhibit 4**) demonstrates that high-dose gp96 effectively blocked anti-tumor immunity generated by gp96 (in the form of gp96-peptide complexes[1] derived from Meth A

[1] Although Chandawarkar does not expressly refer to "complexes" of gp96 and peptide, it would be clear to the skilled worker that complexes are in fact being used

fibrosarcoma) in mice (see Chandawarkar at p. 616, col. 2 to p. 618, col. 1 and Figs. 1 and 2). In Chandawarkar, a high-dose (90 μg) of gp96 derived from Meth A fibrosarcoma or normal liver administered concurrently with an optimal immunizing low-dose (10 μg) of gp96 derived from Meth A fibrosarcoma effectively suppressed tumor immunity of mice challenged with live Meth A cells (see Chandawarkar at p. 616, col. 1 to p. 617, col. 1 and Fig. 1). Further, this immunosuppressive high-dose of gp96 was only effective when it was administered concurrently with or subsequent to the optimal immunizing low-dose of gp96 derived from Meth A fibrosarcoma (see Chandawarkar at p. 617, col. 1 to p. 618, col. 1 and Fig. 2). Thus, the *in vivo* data in Chandawarkar combined with the *in vitro* data in Basu showing that gp96 inhibited an antigen-specific T cell response in an *in vitro* re-presentation assay demonstrate a correlation between the inhibitory activity of gp96 *in vitro* and its ability to inhibit an immune response *in vivo*.

15. In my judgment and opinion, the data described above for gp96, α2M and anti-α2M receptor antibodies demonstrate a correlation between the *in vitro* activity and the *in vivo* activity of compounds that are expected to interfere with the heat shock protein-α2M receptor interaction. Further, in my judgment and opinion, the technical data in the specification of the present application, combined with the post-filing evidence of Binder 2002 (**Exhibit 8**), Binder 2004 (**Exhibit 7**), Basu (**Exhibit 9**), and Chandawarkar (**Exhibit 4**), provide a well-grounded scientific basis (*i.e.*, objective evidence) for the use of the compounds recited in the claims, as antagonists of hsp-α2M receptor binding, for inhibiting an immune response initiated by antigen-hsp complexes, specifically an antigen-specific T cell response, which is an important mechanism in the pathogenesis of autoimmune diseases and disorders.

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because Chandawarkar references Srivastava *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 1986 "Tumor rejection antigens of chemically induced sarcomas of inbred mice," 83:3407-3411, see *e.g.* p. 3408, col. 1 para. 2 to col. 2 para. 4, "Srivastava," enclosed as **Exhibit 10**), for the purification of gp96 (see Chandawarkar at p. 616, col. 1, para. 2). Srivastava teaches the purification of gp96 from the cytosol or soluble membrane fraction of Meth A cells using a combination of affinity and ion-exchange chromatography (*i.e.*, Concavalin A, DEAE-Sepharose, and Mono Q FPLC). By way of clarification, Applicant notes that gp96 is referred to as "Meth A TRA" in Srivastava because it was initially isolated based on its activity as a "Tumor Rejection Antigen." It was known in the art at the time of filing the instant application that the purification method used in Srivastava produces gp96-peptide complexes (see *e.g.*, U.S. Patent No. 5,837,251, issued 11/17/98, at col. 15, line 29 to col. 16, line 47, enclosed as **Exhibit 11**). Thus, the skilled worker would rightly conclude that the gp96 preparations used in Chandawarkar are in fact complexes of gp96 and peptide.

16. The technical data in the specification of the present application supporting the claimed use of the compounds recited in the claims is further supported by the technical data in Chandawarkar (enclosed as **Exhibit 4**) derived by use of various autoimmune disease models. Chandawarkar demonstrates that an antagonist of hsp-α2M receptor interaction, *i.e.*, gp96, effectively inhibits the onset of autoimmune disease in two well-known animals models, the experimental autoimmune encephalomyelitis ("EAE") model, and the non-obese diabetic ("NOD") mouse model. The fact that gp96 is an antagonist of hsp-α2M receptor interaction is demonstrated by Basu, as discussed *supra* in paragraphs 10 and 14. In the EAE model, the autoimmune disease is induced by either myelin basic protein ("MBP") or proteolipid protein ("PLP") (see Chandawarkar at p. 618, col. 2, para. 2-3). Mice were first immunized with MBP and treated with gp96 (in the form of gp96-peptide complexes[2]) obtained from normal mouse liver. Control animals were either left untreated or treated with phosphorylase b (an unrelated protein), saline, or lipopolysaccharide. The results demonstrated that 60-75% of the control animals developed progressive paralysis of all four limbs by day 60-post immunization with MBP. In contrast, only 20-40% of the mice treated with gp96 developed paralysis (see Chandawarkar at p. 618, col. 2, para. 2 and Fig. 3A). Similar results were obtained when EAE was induced using PLP (see Chandawarkar at p. 618, col. 2, para. 3 and Fig. 3B). In the NOD mouse model, mice were immunized twice, one week apart, with gp96 obtained from liver or pancreas of NOD mice (see Chandawarkar at p. 619, col. 1, para. 2). Control animals were treated with phosphate-buffered saline or left untreated. All of the control animals began to develop diabetes between 10 and 14 weeks of age and all were diabetic by 20 weeks of age, as measured by monitoring urine sugar levels (see Chandawarkar at p. 619, col. 1, para. 2-3, and Fig. 4 at p. 620). In contrast, 80% of the mice immunized with 100 μg of gp96 from either liver or pancreas remained disease-free for the entire period of the study, or 24 weeks of age. As noted by Chandawarkar, "[t]he results described in this study show that high-dose gp96 elicits antigen-specific suppression in a wide array of models of immunity, including autoimmunity" (see Chandawarkar at p. 623, col. 1, para. 3). The

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[2] As discussed previously, it would be clear to the skilled worker that gp96-peptide complexes are in fact being used because Chandawarkar references Srivastava *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 1986 "Tumor rejection antigens of chemically induced sarcomas of inbred mice," 83:3407-3411, see *e.g.* p. 3408, col. 1 para. 2 to col. 2 para. 4, "Srivastava," enclosed as **Exhibit 10**), for the purification of gp96 (see Chandawarkar at p. 616, col. 1, para. 2).

immunosuppressive activity of gp96 in this *in vivo* model of autoimmunity further validates the correlation between the inhibitory activity of gp96 *in vitro* and its ability to inhibit an immune response *in vivo*, as discussed in paragraph 14. In my judgment and opinion, these results confirm the data in the specification demonstrating a sound scientific basis for the use of the compounds recited in the claims for treating an autoimmune disease or disorder, because the compounds recited in the claims are, like high-dose gp96, antagonists of the interaction between heat shock protein and the α2M receptor.

17. In my judgment and opinion, the data described above demonstrate a sound scientific basis for the use of the compounds recited in the claims, *i.e.*, an α2M fragment, an α2M receptor fragment, and an antibody specific for the α2M receptor, as antagonists of heat shock protein-α2M receptor binding to block an immune response, including for the treatment of an autoimmune disease or disorder.

18. I declare further that all statements made in this Declaration of my knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: **March 21 2007**

HANS-GEORG RAMMENSEE

Attachments

Exhibit A:	*Curriculum vitae* of Hans-Georg Rammensee
Exhibit 1:	Suto and Srivastava, 1995 "A mechanism for the specific immunogenicity of heat shock protein-chaperoned peptides," *Science* 269:1585-1588 ("Suto")
Exhibit 2:	Abbas, Lichtman, and Pober, 1991 *Cellular and Molecular Immunology*, W.B. Saunders Co., Philadelphia (Chapters 15-18)("Abbas")
Exhibit 3:	Janeway, Travers, Walport, and Shlomchick, 2001 Immunobiology, 5th ed., Garland Publishing, New York (Part V, Sections 13-1 to 13-15) ("Janeway")
Exhibit 4:	Chandawarkar *et al.*, 2004 "Immune modulation with high-dose heat shock protein gp96: therapy of murine autoimmune diabetes and encephalomyelitis," *Int'l Immunol.* 16:315-324 ("Chandawarkar")
Exhibit 5:	Steinman, L. 2001 "Myelin-specific CD8 T cells in the pathogenesis of experimental allergic encephalitits and multiple sclerosis," *J. Exp. Med.* 194:F27-F30 ("Steinman")
Exhibit 6:	SenGupta *et al.*, 2004 "Heat shock protein-mediated cross-presentation of exogenous HIV antigen on HLA Class I and Class II," *J. Immunol.* 173:1987-1993 ("SenGupta")
Exhibit 7:	Binder and Srivastava, 2004 "Essential Role of CD91 in re-presentation of gp96-chaperoned peptides," *Proc. Natl. Acad. Sci. U.S.A.* 6128-6133 ("Binder 2004")
Exhibit 8:	Binder *et al.*, 2002 "Naturally formed or artificially reconstituted non-covalent alpha-2-macroglobulin-peptide complexes elicit CD91-dependent cellular immunity," *Cancer Immunity* 2:16-23 ("Binder 2002")
Exhibit 9:	Basu *et al.*, 2001 "CD91 is a common receptor for heat shock proteins gp96, hsp90, hsp70, and calreticulin," *Immunity* 14:303-313 ("Basu")
Exhibit 10:	Srivastava *et al.* 1986 "Tumor rejection antigens of chemically induced sarcomas of inbred mice," *Proc. Natl. Acad. Sci. U.S.A* 83:3407-3411
Exhibit 11:	U.S. Patent No. 5,837,251, issued November 17, 1998

Curriculum Vitae

Hans-Georg Rammensee

date-of-birth	April 12, 1953 in Tübingen, Germany
parents	Hermann and Irmgard Rammensee
marital status	married, four children
1960-1964	Elementary School in Rottenburg/N, Germany
1964-1972	Eugen Bolz School in Rottenburg/N, Germany
1973-1974	Obligatory Civil Service (work in patient care at the University of Tübingen) including training as an auxiliary in patient care
1974-1980	Study of biology at the University of Tübingen
1974-1980	Night work in patient care at the Radiology Hospital of the University of Tübingen
1980	Biology diploma (graduation)
1980-1982	Ph.D. Thesis ("*Dr. rer. nat.*") awarded by the University of Tübingen for a research project carried out at the Max Planck Institute for Biology on minor histocompatibility antigens (with Professor Dr. Jan Klein)
1983-1985	Postdoctoral position at Scripps Clinic in La Jolla, CA, with M.J. Bevan, supported by the German Research Council. Research on self tolerance of cytotoxic T lymphocytes
1985-1987	Member of the Basel Institute for Immunology. Further work on minor H antigens and self tolerance
1986	Coorganizer, The Tolerance Workshop, Basel
1986 - present	Member of the German Society for Immunology
1987-1993	Group leader at the Department of Immunogenetics, Max Planck Institute for Biology, Tübingen (Director: Professor Dr. Jan Klein)

1987 - present	Editorial Board of *Immunogenetics*
1988	*Heinz Maier Leibnitz Prize* awarded by the German Federal Ministry of Education and Research
1988-1993	Academic teaching at the Universities of Tübingen and Heidelberg
1989-1993	Project supervisor (A8) in the *Sonderforschungsbereich* SFB120 (leukaemia research and immunogenetics) supported by the German Research Council
1991 - 2007	Editorial Board of *European Journal of Immunology*
1991	*Habilitation* (postdoctoral qualification) University of Tübingen
1991	*Wilhelm und Maria Meyenburg Prize* awarded by the German Cancer Research Center, Heidelberg
1991	*Gottfried Wilhelm Leibniz Prize* awarded by the German Research Council
1992	*Avery Landsteiner Prize* awarded by the German Society for Immunology
1992 - 1997	Member of the *Hinterzartener Circle for Cancer Research*, organized by the German Research Council
1993 - 1996	Head of Department, Tumor Virus-Immunology Section, German Cancer Research Center, Heidelberg
1993 - 1996	Appointment as Professor, University of Heidelberg, Faculty of Theoretical Medicine
1993	*Robert Koch Prize* awarded by the Robert Koch Foundation
1996	*Paul Ehrlich and Ludwig Darmstaedter Prize* awarded by the Paul Ehrlich Foundation
1996 - present	Appointment as Chair of Immunology at the University of Tübingen, Head of the Department of Immunology and Director of the Interfacultary Institute for Cell Biology
1997 – 2001	Chairman of the *Graduiertenkolleg Zellbiologie in der Medizin* (Graduate School for Cell Biology in Medicine) supported by the German Research Council.

1997	*Rose Payne Distinguished Scientist Award* of the American Society for Histocompatibility and Immunogenetics
1997 - 2004	Vice Chairman and Chairman of the *Sonderforschungsbereich 510 Hemopoietic Stem Cell Biology and Antigen Processing* supported by the German Research Council
1998 - present	Member of the Evaluation Committee for the Cooperation Program in Cancer Research between the German Cancer Research Center (Heidelberg) and the Ministry of Science, Israel
2000 – present	Member of the Advisory Board and the Board of Management, Medical Faculty, University of Tübingen and Dean for research affairs
2000	Co-founder of the biotechnology enterprise *immatics biotechnologies GmbH* and Head of the Scientific Advisory Board
2000	Co-founder of the biotechnology enterprise *Curevac GmbH* and Scientific Director of Immunology
2001	Co-founder of the *Verein zur Förderung der Biotechnologie Stuttgart/Tübingen/Neckar-Alb e.V.* (Association for the Advancement of Biotechnology in Stuttgart/Tübingen/Neckar-Alb)
2002 – present	Member of the Academy of Cancer Immunology: Editorial Board of *Cancer Immunity*
2002 - present	Chairman of the *Graduiertenkolleg Zellbiologische Mechanismen immunassoziierter Prozesse 794* (Graduate School for Cellular Mechanisms of Immune-associated Processes) supported by the German Research Council
2002	Co-founder and association member of the Association for Cancer Immunotherapy (CIMT) (*Kompetenznetzwerk Immunologische Krebs-Therapie e.V.)*
06/2004 - present	Member of the Editorial Board of *Current Immunology Reviews*
2005 -	Chairman of the *Sonderforschungsbereich 685: Immunotherapy: molecular basis and clinical application* financed by the German Research Council
2006 -	Member, Academy of Science and Literature, Mainz
2006 -	Panel Member, Scientific Council of the European Research Council

March 2007